C10 HETEROSUBSTITUTED ACETATE TAXANES

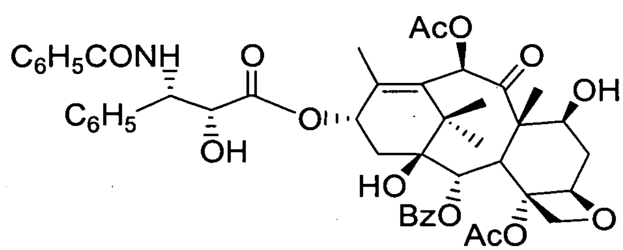
CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Serial No. 09/775,912 filed February 2, 2001, which claimed priority from U.S. provisional application Serial No. 60/179,669, filed on February 2, 2000.

BACKGROUND OF THE INVENTION

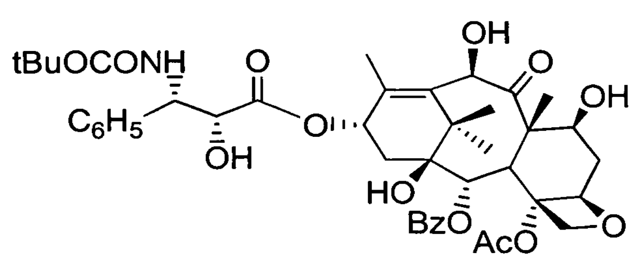
The present invention is directed to novel taxanes which have exceptional utility as antitumor agents.

The taxane family of terpenes, of which baccatin III and taxol are members, has been the subject of considerable interest in both the biological and chemical arts. Taxol itself is employed as a cancer chemotherapeutic agent and possesses a broad range of tumor-inhibiting activity. Taxol has a 2′R, 3′S configuration and the following structural formula:



wherein Ac is acetyl.

Colin et al. reported in U.S. Patent 4,814,470 that certain taxol analogs have an activity significantly greater than that of taxol. One of these analogs, commonly referred to as docetaxel, has the following structural formula:



Although taxol and docetaxel are useful chemotherapeutic agents, there are limitations on their effectiveness, including limited efficacy against certain types of cancers and toxicity to subjects when administered at various doses. Accordingly, a need remains for additional chemotherapeutic agents with improved efficacy and less toxicity.

SUMMARY OF THE INVENTION

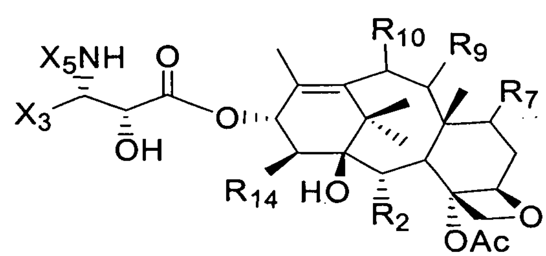
Among the objects of the present invention, therefore, is the provision of taxanes which compare favorably to taxol and docetaxel with respect to efficacy as anti-tumor agents and with respect to toxicity. In general, these taxanes possess a heterosubstituted acetate substituent at C-10, a hydroxy substituent at C-7 and a range of C-3' substituents.

Briefly, therefore, the present invention is directed to the taxane composition, per se, to pharmaceutical compositions comprising the taxane and a pharmaceutically acceptable carrier, and to methods of administration.

Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In one embodiment of the present invention, the taxanes of the present invention correspond to structure (1):



(1)

wherein

R_2 is acyloxy;

R_7 is hydroxy;

R_9 is keto, hydroxy, or acyloxy;

R_{10} is heterosubstituted acetate;

R_{14} is hydrido or hydroxy;

X_3 is substituted or unsubstituted alkyl, alkenyl, alkynyl, phenyl or heterocyclo;

X_5 is $-COX_{10}$, $-COOX_{10}$, or $-CONHX_{10}$;

X_{10} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo;

Ac is acetyl; and

R_7, R_9, and R_{10} independently have the alpha or beta stereochemical configuration.

In one embodiment, R_2 is an ester ($R_{2a}C(O)O-$), a carbamate ($R_{2a}R_{2b}NC(O)O-$), a carbonate ($R_{2a}OC(O)O-$), or a thiocarbamate ($R_{2a}SC(O)O-$) wherein R_{2a} and R_{2b} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl or heterocyclo. In a preferred embodiment, R_2 is an ester ($R_{2a}C(O)O-$), wherein R_{2a} is aryl or heteroaromatic. In another preferred embodiment, R_2 is an ester ($R_{2a}C(O)O-$), wherein R_{2a} is substituted or unsubstituted phenyl, furyl, thienyl, or pyridyl. In one particularly preferred embodiment, R_2 is benzoyloxy.

While R_9 is keto in one embodiment of the present invention, in other embodiments R_9 may have the alpha or beta stereochemical configuration, preferably the beta stereochemical configuration, and may be, for example, α- or β-hydroxy or α- or β-acyloxy. For example, when R_9 is acyloxy, it may be an ester ($R_{9a}C(O)O-$), a carbamate ($R_{9a}R_{9b}NC(O)O-$), a carbonate ($R_{9a}OC(O)O-$), or a thiocarbamate ($R_{9a}SC(O)O-$) wherein R_{9a} and R_{9b} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl or heterocyclo. If R_9 is an ester ($R_{9a}C(O)O-$), R_{9a} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaromatic. Still more preferably, R_9 is an ester ($R_{9a}C(O)O-$), wherein R_{9a} is substituted or unsubstituted phenyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, or substituted or unsubstituted pyridyl. In one embodiment R_9 is ($R_{9a}C(O)O-$) wherein R_{9a} is methyl, ethyl, propyl (straight, branched or cyclic), butyl (straight, branched or cyclic), pentyl, (straight, branched or cyclic), or hexyl (straight, branched or cyclic). In another embodiment R_9 is ($R_{9a}C(O)O-$) wherein R_{9a} is substituted methyl, substituted ethyl, substituted propyl (straight, branched or cyclic), substituted butyl (straight, branched or cyclic), substituted pentyl, (straight, branched or cyclic), or substituted hexyl (straight, branched or cyclic)

wherein the substituent(s) is/are selected from the group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.

In one embodiment, R_{10} is $R_{10a}C(O)O$- wherein R_{10a} is heterosubstituted methyl, said heterosubstituted methyl moiety lacking a carbon atom which is in the beta position relative to the carbon atom of which R_{10a} is a substituent. The heterosubstituted methyl is covalently bonded to at least one heteroatom and optionally with hydrogen, the heteroatom being, for example, a nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or halogen atom. The heteroatom may, in turn, be substituted with other atoms to form a heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, oxy, acyloxy, nitro, amino, amido, thiol, ketals, acetals, esters or ether moiety. Exemplary R_{10} substituents include $R_{10a}COO$- wherein R_{10a} is chloromethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, acetoxymethyl, acyloxymethyl, or methylthiomethyl.

Exemplary X_3 substituents include substituted or unsubstituted C_2 to C_8 alkyl, substituted or unsubstituted C_2 to C_8 alkenyl, substituted or unsubstituted C_2 to C_8 alkynyl, substituted or unsubstituted heteroaromatics containing 5 or 6 ring atoms, and substituted or unsubstituted phenyl. Exemplary preferred X_3 substituents include substituted or unsubstituted ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclohexyl, isobutenyl, furyl, thienyl, and pyridyl.

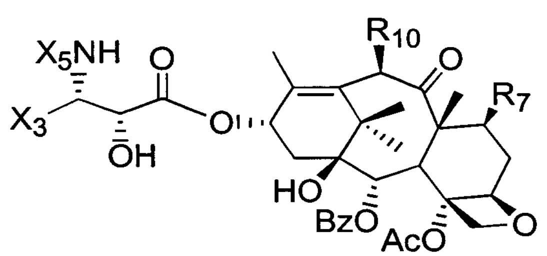
Exemplary X_5 substituents include $-COX_{10}$, $-COOX_{10}$ or $-CONHX_{10}$ wherein X_{10} is substituted or unsubstituted alkyl, alkenyl, phenyl or heteroaromatic. Exemplary preferred X_5 substituents include $-COX_{10}$, $-COOX_{10}$ or $-CONHX_{10}$ wherein X_{10} is (i) substituted or unsubstituted C_1 to C_8 alkyl such as substituted or unsubstituted methyl, ethyl, propyl (straight, branched or cyclic), butyl (straight, branched or cyclic), pentyl (straight, branched or cyclic), or hexyl (straight, branched or cyclic); (ii) substituted or unsubstituted C_2 to C_8 alkenyl such as substituted or unsubstituted ethenyl, propenyl (straight, branched or cyclic), butenyl (straight, branched or cyclic), pentenyl (straight, branched or cyclic) or hexenyl (straight, branched or cyclic); (iii) substituted or unsubstituted C_2 to C_8 alkynyl such as substituted or unsubstituted ethynyl, propynyl (straight or branched), butynyl (straight or branched), pentynyl (straight or branched), or hexynyl (straight or branched); (iv) substituted or unsubstituted phenyl, or (v)

substituted or unsubstituted heteroaromatic such as furyl, thienyl, or pyridyl, wherein the substituent(s) is/are selected from the group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.

In one embodiment of the present invention, the taxane corresponds to structure 1, X_5 is -COX_{10} wherein X_{10} is phenyl or -$COOX_{10}$ wherein X_{10} is t-butoxycarbonyl, and R_{10} is $R_{10a}C(O)O$- wherein R_{10a} is alkoxymethyl, preferably methoxymethyl or ethoxymethyl. In another embodiment of the present invention the taxane corresponds to structure 1, X_5 is -COX_{10} wherein X_{10} is phenyl or -$COOX_{10}$ wherein X_{10} is t-butoxycarbonyl, and R_{10} is $R_{10a}C(O)O$- wherein R_{10a} is acyloxymethyl, preferably acetoxymethyl.

In another embodiment of the present invention, the taxane corresponds to structure 1, X_5 is -COX_{10} wherein X_{10} is phenyl or -$COOX_{10}$ wherein X_{10} is t-butoxycarbonyl, R_{10} is $R_{10a}C(O)O$- wherein R_{10a} is alkoxymethyl such as methoxymethyl or ethoxymethyl, or aryloxymethyl such as phenoxymethyl, and X_3 is heterocyclo. In another embodiment of the present invention the taxane corresponds to structure 1, X_5 is -COX_{10} wherein X_{10} is phenyl or -$COOX_{10}$ wherein X_{10} is t-butoxycarbonyl, and R_{10} is $R_{10a}C(O)O$- wherein R_{10a} is acyloxymethyl, preferably acetoxymethyl, and X_3 is heterocyclo.

In one preferred embodiment of the present invention, the taxanes of the present invention correspond to structure (2):



(2)

wherein

R_7 is hydroxy;

R_{10} is heterosubstituted acetate;

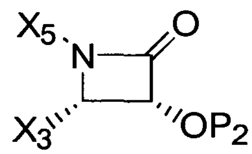
X_3 is substituted or unsubstituted alkyl, alkenyl, alkynyl, or heterocyclo, wherein alkyl comprises at least two carbon atoms;

X_5 is $-COX_{10}$, $-COOX_{10}$, or $-CONHX_{10}$; and

X_{10} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo.

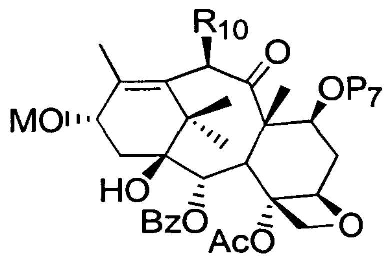
For example, in this preferred embodiment in which the taxane corresponds to structure (2), R_{10} is $R_{10a}COO$- wherein R_{10a} is heterosubstituted methyl, more preferably heterosubstituted methyl wherein the heterosubsituents are selected from the group consisting of nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or halogen atoms, still more preferably heterosubstituted methyl wherein the heterosubstituent is alkoxy or acyloxy. While R_{10a} is selected from among these, in one embodiment X_3 is selected from substituted or unsubstituted alkyl, alkenyl, phenyl or heterocyclo, more preferably substituted or unsubstituted alkenyl, phenyl or heterocyclo, still more preferably substituted or unsubstituted phenyl or heterocyclo, and still more preferably heterocyclo such as furyl, thienyl or pyridyl. While R_{10a} and X_3 are selected from among these, in one embodiment X_5 is selected from $-COX_{10}$ wherein X_{10} is phenyl, alkyl or heterocyclo, more preferably phenyl. Alternatively, while R_{10a} and X_3 are selected from among these, in one embodiment X_5 is selected from $-COX_{10}$ wherein X_{10} is phenyl, alkyl or heterocyclo, more preferably phenyl, or X_5 is $-COOX_{10}$ wherein X_{10} is alkyl, preferably t-butyl. Among the more preferred embodiments, therefore, are taxanes corresponding to structure 2 in which (i) X_5 is $-COOX_{10}$ wherein X_{10} is tert-butyl or X_5 is $-COX_{10}$ wherein X_{10} is phenyl, (ii) X_3 is substituted or unsubstituted cycloalkyl, alkenyl, phenyl or heterocyclo, more preferably substituted or unsubstituted isobutenyl, phenyl, furyl, thienyl, or pyridyl, still more preferably unsubstituted isobutenyl, furyl, thienyl or pyridyl, and (iii) R_{10} is alkoxyacetyl aryloxyacetyl, or acyloxyacetyl.

Taxanes having the general formula 1 may be obtained by treatment of a b-lactam with an alkoxide having the taxane tetracyclic nucleus and a C-13 metallic oxide substituent to form compounds having a b-amido ester substituent at C-13 (as described more fully in Holton U.S. Patent 5,466,834), followed by removal of the hydroxy protecting groups. The β-lactam has the following structural formula (3):



(3)

wherein P_2 is a hydroxy protecting group and X_3 and X_5 are as previously defined and the alkoxide has the structural formula (4):



(4)

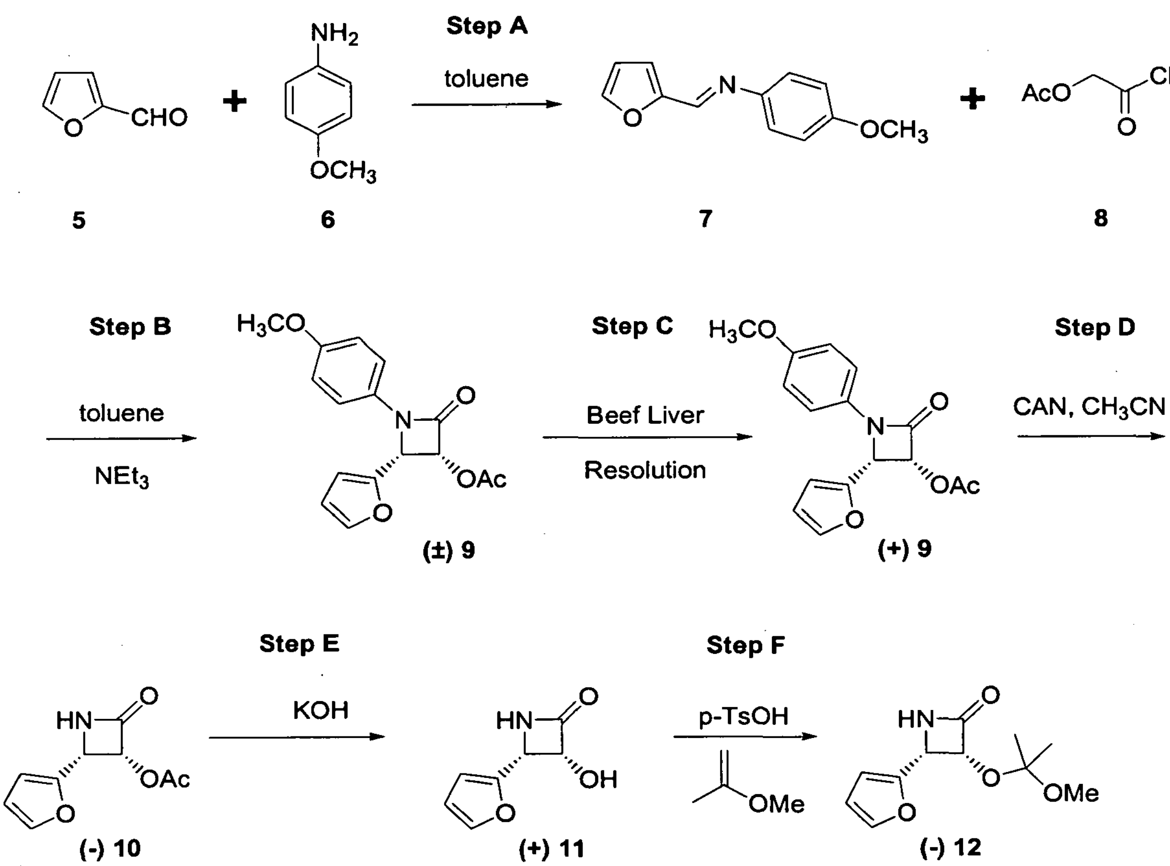
wherein M is a metal or ammonium, P_7 is a hydroxy protecting group and R_{10} is as previously defined. The alkoxide may be prepared from 10-deacetylbaccatin III by selective esterification of the C-10 hydroxyl group and then protection of the C-7 hydroxyl group (as described more fully in Holton et al., PCT Patent Application WO 99/09021) followed by treatment with a metallic amide.

Alternatively, taxanes having the general formula 1 may be obtained by treatment of a b-lactam with an alkoxide having the taxane tetracyclic nucleus and a C-13 metallic oxide substituent to form compounds having a b-amido ester substituent at C-13 (as described more fully in Holton U.S. Patent 5,466,834), followed by selective deprotection of the C(10) hydroxy group and reaction with an acylating agent such as an alkoxyacetyl halide.

Derivatives of 10-deacetylbaccatin III having alternative substituents at C(2), C(9) and C(14) and processes for their preparation are known in the art. Taxane derivatives having acyloxy substituents other than benzoyloxy at C(2) may be prepared, for example, as described in Holton et al., U.S. Patent No. 5,728,725 or Kingston et al., U.S. Patent No. 6,002,023. Taxanes having acyloxy or hydroxy substituents at C(9) in place of keto may be prepared, for example as described in Holton et al., U.S. Patent No. 6,011,056 or Gunawardana et al., U.S.

Patent No. 5,352,806. Taxanes having a beta hydroxy substituent at C(14) may be prepared from naturally occurring 14-hydroxy-10-deacetylbaccatin III.

Processes for the preparation and resolution of the β-lactam starting material are generally well known. For example, the β-lactam may be prepared as described in Holton, U.S. Patent No. 5,430,160 and the resulting enatiomeric mixtures of β-lactams may be resolved by a stereoselective hydrolysis using a lipase or enzyme as described, for example, in Patel, U.S. Patent No. 5,879,929 Patel U.S. Patent No. 5,567,614 or a liver homogenate as described, for example, in PCT Patent Application No. 00/41204. In a preferred embodiment in which the β-lactam is furyl substituted at the C(4) position, the β-lactam can be prepared as illustrated in the following reaction scheme:



wherein Ac is acetyl, NEt_3 is triethylamine, CAN is ceric ammonium nitrate, and p-TsOH is p-toluenesulfonic acid. The beef liver resolution may be carried out, for

example, by combining the enatiomeric β-lactam mixture with a beef liver suspension (prepared, for example, by adding 20 g of frozen beef liver to a blender and then adding a pH 8 buffer to make a total volume of 1 L).

Compounds of formula 1 of the instant invention are useful for inhibiting tumor growth in mammals including humans and are preferably administered in the form of a pharmaceutical composition comprising an effective antitumor amount of a compound of the instant invention in combination with at least one pharmaceutically or pharmacologically acceptable carrier. The carrier, also known in the art as an excipient, vehicle, auxiliary, adjuvant, or diluent, is any substance which is pharmaceutically inert, confers a suitable consistency or form to the composition, and does not diminish the therapeutic efficacy of the antitumor compounds. The carrier is "pharmaceutically or pharmacologically acceptable" if it does not produce an adverse, allergic or other untoward reaction when administered to a mammal or human, as appropriate.

The pharmaceutical compositions containing the antitumor compounds of the present invention may be formulated in any conventional manner. Proper formulation is dependent upon the route of administration chosen. The compositions of the invention can be formulated for any route of administration so long as the target tissue is available via that route. Suitable routes of administration include, but are not limited to, oral, parenteral (e.g., intravenous, intraarterial, subcutaneous, rectal, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intraperitoneal, or intrasternal), topical (nasal, transdermal, intraocular), intravesical, intrathecal, enteral, pulmonary, intralymphatic, intracavital, vaginal, transurethral, intradermal, aural, intramammary, buccal, orthotopic, intratracheal, intralesional, percutaneous, endoscopical, transmucosal, sublingual and intestinal administration.

Pharmaceutically acceptable carriers for use in the compositions of the present invention are well known to those of ordinary skill in the art and are selected based upon a number of factors: the particular antitumor compound used, and its concentration, stability and intended bioavailability; the disease, disorder or condition being treated with the composition; the subject, its age, size and general condition; and the route of administration. Suitable carriers are readily determined by one of ordinary skill in the art (see, for example, J. G. Nairn, in: Remington's Pharmaceutical Science (A. Gennaro, ed.), Mack Publishing Co.,

Easton, Pa., (1985), pp. 1492-1517, the contents of which are incorporated herein by reference).

The compositions are preferably formulated as tablets, dispersible powders, pills, capsules, gelcaps, caplets, gels, liposomes, granules, solutions, suspensions, emulsions, syrups, elixirs, troches, dragees, lozenges, or any other dosage form which can be administered orally. Techniques and compositions for making oral dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976).

The compositions of the invention for oral administration comprise an effective antitumor amount of a compound of the invention in a pharmaceutically acceptable carrier. Suitable carriers for solid dosage forms include sugars, starches, and other conventional substances including lactose, talc, sucrose, gelatin, carboxymethylcellulose, agar, mannitol, sorbitol, calcium phosphate, calcium carbonate, sodium carbonate, kaolin, alginic acid, acacia, corn starch, potato starch, sodium saccharin, magnesium carbonate, tragacanth, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, and stearic acid. Further, such solid dosage forms may be uncoated or may be coated by known techniques; e.g., to delay disintegration and absorption.

The antitumor compounds of the present invention are also preferably formulated for parenteral administration, e.g., formulated for injection via intravenous, intraarterial, subcutaneous, rectal, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intraperitoneal, or intrasternal routes. The compositions of the invention for parenteral administration comprise an effective antitumor amount of the antitumor compound in a pharmaceutically acceptable carrier. Dosage forms suitable for parenteral administration include solutions, suspensions, dispersions, emulsions or any other dosage form which can be administered parenterally. Techniques and compositions for making parenteral dosage forms are known in the art.

Suitable carriers used in formulating liquid dosage forms for oral or parenteral administration include nonaqueous, pharmaceutically-acceptable polar

solvents such as oils, alcohols, amides, esters, ethers, ketones, hydrocarbons and mixtures thereof, as well as water, saline solutions, dextrose solutions (e.g., DW5), electrolyte solutions, or any other aqueous, pharmaceutically acceptable liquid.

Suitable nonaqueous, pharmaceutically-acceptable polar solvents include, but are not limited to, alcohols (e.g., α-glycerol formal, β-glycerol formal, 1, 3-butyleneglycol, aliphatic or aromatic alcohols having 2-30 carbon atoms such as methanol, ethanol, propanol, isopropanol, butanol, t-butanol, hexanol, octanol, amylene hydrate, benzyl alcohol, glycerin (glycerol), glycol, hexylene glycol, tetrahydrofurfuryl alcohol, lauryl alcohol, cetyl alcohol, or stearyl alcohol, fatty acid esters of fatty alcohols such as polyalkylene glycols (e.g., polypropylene glycol, polyethylene glycol), sorbitan, sucrose and cholesterol); amides (e.g., dimethylacetamide (DMA), benzyl benzoate DMA, dimethylformamide, N-(β-hydroxyethyl)-lactamide, N, N-dimethylacetamide_amides, 2-pyrrolidinone, 1-methyl-2-pyrrolidinone, or polyvinylpyrrolidone); esters (e.g., 1-methyl-2-pyrrolidinone, 2-pyrrolidinone, acetate esters such as monoacetin, diacetin, and triacetin, aliphatic or aromatic esters such as ethyl caprylate or octanoate, alkyl oleate, benzyl benzoate, benzyl acetate, dimethylsulfoxide (DMSO), esters of glycerin such as mono, di, or tri-glyceryl citrates or tartrates, ethyl benzoate, ethyl acetate, ethyl carbonate, ethyl lactate, ethyl oleate, fatty acid esters of sorbitan, fatty acid derived PEG esters, glyceryl monostearate, glyceride esters such as mono, di, or tri-glycerides, fatty acid esters such as isopropyl myristrate, fatty acid derived PEG esters such as PEG-hydroxyoleate and PEG-hydroxystearate, N-methyl pyrrolidinone, pluronic 60, polyoxyethylene sorbitol oleic polyesters such as poly(ethoxylated)$_{30\text{-}60}$ sorbitol poly(oleate)$_{2\text{-}4,}$ poly(oxyethylene)$_{15\text{-}20}$ monooleate, poly(oxyethylene)$_{15\text{-}20}$ mono 12-hydroxystearate, and poly(oxyethylene)$_{15\text{-}20}$ mono ricinoleate, polyoxyethylene sorbitan esters such as polyoxyethylene-sorbitan monooleate, polyoxyethylene-sorbitan monopalmitate, polyoxyethylene-sorbitan monolaurate, polyoxyethylene-sorbitan monostearate, and Polysorbate® 20, 40, 60 or 80 from ICI Americas, Wilmington, DE, polyvinylpyrrolidone, alkyleneoxy modified fatty acid esters such as polyoxyl 40 hydrogenated castor oil and polyoxyethylated castor oils (e.g., Cremophor® EL solution or Cremophor® RH 40 solution), saccharide fatty acid esters (i.e., the condensation product of a monosaccharide (e.g., pentoses such as ribose, ribulose, arabinose, xylose,

lyxose and xylulose, hexoses such as glucose, fructose, galactose, mannose and sorbose, trioses, tetroses, heptoses, and octoses), disaccharide (e.g., sucrose, maltose, lactose and trehalose) or oligosaccharide or mixture thereof with a C_4-C_{22} fatty acid(s)(e.g., saturated fatty acids such as caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid and stearic acid, and unsaturated fatty acids such as palmitoleic acid, oleic acid, elaidic acid, erucic acid and linoleic acid)), or steroidal esters); alkyl, aryl, or cyclic ethers having 2-30 carbon atoms (e.g., diethyl ether, tetrahydrofuran, dimethyl isosorbide, diethylene glycol monoethyl ether); glycofurol (tetrahydrofurfuryl alcohol polyethylene glycol ether); ketones having 3-30 carbon atoms (e.g., acetone, methyl ethyl ketone, methyl isobutyl ketone); aliphatic, cycloaliphatic or aromatic hydrocarbons having 4-30 carbon atoms (e.g., benzene, cyclohexane, dichloromethane, dioxolanes, hexane, n-decane, n-dodecane, n-hexane, sulfolane, tetramethylenesulfon, tetramethylenesulfoxide, toluene, dimethylsulfoxide (DMSO), or tetramethylenesulfoxide); oils of mineral, vegetable, animal, essential or synthetic origin (e.g., mineral oils such as aliphatic or wax-based hydrocarbons, aromatic hydrocarbons, mixed aliphatic and aromatic based hydrocarbons, and refined paraffin oil, vegetable oils such as linseed, tung, safflower, soybean, castor, cottonseed, groundnut, rapeseed, coconut, palm, olive, corn, corn germ, sesame, persic and peanut oil and glycerides such as mono-, di- or triglycerides, animal oils such as fish, marine, sperm, cod-liver, haliver, squalene, squalane, and shark liver oil, oleic oils, and polyoxyethylated castor oil); alkyl or aryl halides having 1-30 carbon atoms and optionally more than one halogen substituent; methylene chloride; monoethanolamine; petroleum benzin; trolamine; omega-3 polyunsaturated fatty acids (e.g., alpha-linolenic acid, eicosapentaenoic acid, docosapentaenoic acid, or docosahexaenoic acid); polyglycol ester of 12-hydroxystearic acid and polyethylene glycol (Solutol® HS-15, from BASF, Ludwigshafen, Germany); polyoxyethylene glycerol; sodium laurate; sodium oleate; or sorbitan monooleate.

Other pharmaceutically acceptable solvents for use in the invention are well known to those of ordinary skill in the art, and are identified in The Chemotherapy Source Book (Williams & Wilkens Publishing), The Handbook of Pharmaceutical Excipients, (American Pharmaceutical Association, Washington, D.C., and The Pharmaceutical Society of Great Britain, London, England, 1968),

Modern Pharmaceutics, (G. Banker et al., eds., 3d ed.)(Marcel Dekker, Inc., New York, New York, 1995), The Pharmacological Basis of Therapeutics, (Goodman & Gilman, McGraw Hill Publishing), Pharmaceutical Dosage Forms, (H. Lieberman et al., eds.,)(Marcel Dekker, Inc., New York, New York, 1980), Remington's Pharmaceutical Sciences (A. Gennaro, ed., 19th ed.)(Mack Publishing, Easton, PA, 1995), The United States Pharmacopeia 24, The National Formulary 19, (National Publishing, Philadelphia, PA, 2000), A.J. Spiegel et al., and Use of Nonaqueous Solvents in Parenteral Products, JOURNAL OF PHARMACEUTICAL SCIENCES, Vol. 52, No. 10, pp. 917-927 (1963).

Preferred solvents include those known to stabilize the antitumor compounds, such as oils rich in triglycerides, for example, safflower oil, soybean oil or mixtures thereof, and alkyleneoxy modified fatty acid esters such as polyoxyl 40 hydrogenated castor oil and polyoxyethylated castor oils (e.g., Cremophor® EL solution or Cremophor® RH 40 solution). Commercially available triglycerides include Intralipid® emulsified soybean oil (Kabi-Pharmacia Inc., Stockholm, Sweden), Nutralipid ® emulsion (McGaw, Irvine, California), Liposyn® II 20% emulsion (a 20% fat emulsion solution containing 100 mg safflower oil, 100 mg soybean oil, 12 mg egg phosphatides, and 25 mg glycerin per ml of solution; Abbott Laboratories, Chicago, Illinois), Liposyn® III 2% emulsion (a 2% fat emulsion solution containing 100 mg safflower oil, 100 mg soybean oil, 12 mg egg phosphatides, and 25 mg glycerin per ml of solution; Abbott Laboratories, Chicago, Illinois), natural or synthetic glycerol derivatives containing the docosahexaenoyl group at levels between 25% and 100% by weight based on the total fatty acid content (Dhasco® (from Martek Biosciences Corp., Columbia, MD), DHA Maguro® (from Daito Enterprises, Los Angeles, CA), Soyacal®, and Travemulsion®. Ethanol is a preferred solvent for use in dissolving the antitumor compound to form solutions, emulsions, and the like.

Additional minor components can be included in the compositions of the invention for a variety of purposes well known in the pharmaceutical industry. These components will for the most part impart properties which enhance retention of the antitumor compound at the site of administration, protect the stability of the composition, control the pH, facilitate processing of the antitumor compound into pharmaceutical formulations, and the like. Preferably, each of these components is individually present in less than about 15 weight % of the

total composition, more preferably less than about 5 weight %, and most preferably less than about 0.5 weight % of the total composition. Some components, such as fillers or diluents, can constitute up to 90 wt.% of the total composition, as is well known in the formulation art. Such additives include cryoprotective agents for preventing reprecipitation of the taxane, surface active, wetting or emulsifying agents (e.g., lecithin, polysorbate-80, Tween® 80, pluronic 60, polyoxyethylene stearate), preservatives (e.g., ethyl-p-hydroxybenzoate), microbial preservatives (e.g., benzyl alcohol, phenol, m-cresol, chlorobutanol, sorbic acid, thimerosal and paraben), agents for adjusting pH or buffering agents (e.g., acids, bases, sodium acetate, sorbitan monolaurate), agents for adjusting osmolarity (e.g., glycerin), thickeners (e.g., aluminum monostearate, stearic acid, cetyl alcohol, stearyl alcohol, guar gum, methyl cellulose, hydroxypropylcellulose, tristearin, cetyl wax esters, polyethylene glycol), colorants, dyes, flow aids, non-volatile silicones (e.g., cyclomethicone), clays (e.g., bentonites), adhesives, bulking agents, flavorings, sweeteners, adsorbents, fillers (e.g., sugars such as lactose, sucrose, mannitol, or sorbitol, cellulose, or calcium phosphate), diluents (e.g., water, saline, electrolyte solutions), binders (e.g., starches such as maize starch, wheat starch, rice starch, or potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, sugars, polymers, acacia), disintegrating agents (e.g., starches such as maize starch, wheat starch, rice starch, potato starch, or carboxymethyl starch, cross-linked polyvinyl pyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate, croscarmellose sodium or crospovidone), lubricants (e.g., silica, talc, stearic acid or salts thereof such as magnesium stearate, or polyethylene glycol), coating agents (e.g., concentrated sugar solutions including gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, or titanium dioxide), and antioxidants (e.g., sodium metabisulfite, sodium bisulfite, sodium sulfite, dextrose, phenols, and thiophenols).

In a preferred embodiment, a pharmaceutical composition of the invention comprises at least one nonaqueous, pharmaceutically acceptable solvent and an antitumor compound having a solubility in ethanol of at least about 100, 200, 300, 400, 500, 600, 700 or 800 mg/ml. While not being bound to a particular theory, it is believed that the ethanol solubility of the antitumor compound may be directly

related to its efficacy. The antitumor compound can also be capable of being crystallized from a solution. In other words, a crystalline antitumor compound, such as compound 1393, can be dissolved in a solvent to form a solution and then recrystallized upon evaporation of the solvent without the formation of any amorphous antitumor compound. It is also preferred that the antitumor compound have an ID50 value (i.e, the drug concentration producing 50% inhibition of colony formation) of at least 4, 5, 6, 7, 8, 9, or 10 times less that of paclitaxel when measured according to the protocol set forth in the working examples.

Dosage form administration by these routes may be continuous or intermittent, depending, for example, upon the patient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to and assessable by a skilled practitioner.

Dosage and regimens for the administration of the pharmaceutical compositions of the invention can be readily determined by those with ordinary skill in treating cancer. It is understood that the dosage of the antitumor compounds will be dependent upon the age, sex, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. For any mode of administration, the actual amount of antitumor compound delivered, as well as the dosing schedule necessary to achieve the advantageous effects described herein, will also depend, in part, on such factors as the bioavailability of the antitumor compound, the disorder being treated, the desired therapeutic dose, and other factors that will be apparent to those of skill in the art. The dose administered to an animal, particularly a human, in the context of the present invention should be sufficient to effect the desired therapeutic response in the animal over a reasonable period of time. Preferably, an effective amount of the antitumor compound, whether administered orally or by another route, is any amount which would result in a desired therapeutic response when administered by that route. Preferably, the compositions for oral administration are prepared in such a way that a single dose in one or more oral preparations contains at least 20 mg of the antitumor compound per m^2 of patient body surface area, or at least 50, 100, 150, 200, 300, 400, or 500 mg of the antitumor compound per m^2 of patient body surface area, wherein the average body surface area for a human is 1.8 m^2. Preferably, a

single dose of a composition for oral administration contains from about 20 to about 600 mg of the antitumor compound per m^2 of patient body surface area, more preferably from about 25 to about 400 mg/m^2, even more preferably, from about 40 to about 300 mg/m^2, and even more preferably from about 50 to about 200 mg/m^2. Preferably, the compositions for parenteral administration are prepared in such a way that a single dose contains at least 20 mg of the antitumor compound per m^2 of patient body surface area, or at least 40, 50, 100, 150, 200, 300, 400, or 500 mg of the antitumor compound per m^2 of patient body surface area. Preferably, a single dose in one or more parenteral preparations contains from about 20 to about 500 mg of the antitumor compound per m^2 of patient body surface area, more preferably from about 40 to about 400 mg/m^2, and even more preferably, from about 60 to about 350 mg/m^2. However, the dosage may vary depending on the dosing schedule which can be adjusted as necessary to achieve the desired therapeutic effect. It should be noted that the ranges of effective doses provided herein are not intended to limit the invention and represent preferred dose ranges. The most preferred dosage will be tailored to the individual subject, as is understood and determinable by one of ordinary skill in the art without undue experimentation.

The concentration of the antitumor compound in a liquid pharmaceutical composition is preferably between about 0.01 mg and about 10 mg per ml of the composition, more preferably between about 0.1 mg and about 7 mg per ml, even more preferably between about 0.5 mg and about 5 mg per ml, and most preferably between about 1.5 mg and about 4 mg per ml. Relatively low concentrations are generally preferred because the antitumor compound is most soluble in the solution at low concentrations. The concentration of the antitumor compound in a solid pharmaceutical composition for oral administration is preferably between about 5 weight % and about 50 weight %, based on the total weight of the composition, more preferably between about 8 weight % and about 40 weight %, and most preferably between about 10 weight % and about 30 weight %.

In one embodiment, solutions for oral administration are prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g., ethanol or methylene chloride) to form a solution. An appropriate volume of a carrier which is a solution, such as

Cremophor® EL solution, is added to the solution while stirring to form a pharmaceutically acceptable solution for oral administration to a patient. If desired, such solutions can be formulated to contain a minimal amount of, or to be free of, ethanol, which is known in the art to cause adverse physiological effects when administered at certain concentrations in oral formulations.

In another embodiment, powders or tablets for oral administration are prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g.,ethanol or methylene chloride) to form a solution. The solvent can optionally be capable of evaporating when the solution is dried under vacuum. An additional carrier can be added to the solution prior to drying, such as Cremophor® EL solution. The resulting solution is dried under vacuum to form a glass. The glass is then mixed with a binder to form a powder. The powder can be mixed with fillers or other conventional tabletting agents and processed to form a tablet for oral administration to a patient. The powder can also be added to any liquid carrier as described above to form a solution, emulsion, suspension or the like for oral administration.

Emulsions for parenteral administration can be prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g., ethanol or methylene chloride) to form a solution. An appropriate volume of a carrier which is an emulsion, such as Liposyn® II or Liposyn® III emulsion, is added to the solution while stirring to form a pharmaceutically acceptable emulsion for parenteral administration to a patient. If desired, such emulsions can be formulated to contain a minimal amount of, or to be free of, ethanol or Cremophor® solution, which are known in the art to cause adverse physiological effects when administered at certain concentrations in parenteral formulations.

Solutions for parenteral administration can be prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g., ethanol or methylene chloride) to form a solution. An appropriate volume of a carrier which is a solution, such as Cremophor® solution, is added to the solution while stirring to form a pharmaceutically acceptable solution for parenteral administration to a patient. If desired, such solutions can be formulated to contain a minimal amount of, or to be free of,

ethanol or Cremophor® solution, which are known in the art to cause adverse physiological effects when administered at certain concentrations in parenteral formulations.

If desired, the emulsions or solutions described above for oral or parenteral administration can be packaged in IV bags, vials or other conventional containers in concentrated form and diluted with any pharmaceutically acceptable liquid, such as saline, to form an acceptable taxane concentration prior to use as is known in the art.

Definitions

The terms "hydrocarbon" and "hydrocarbyl" as used herein describe organic compounds or radicals consisting exclusively of the elements carbon and hydrogen. These moieties include alkyl, alkenyl, alkynyl, and aryl moieties. These moieties also include alkyl, alkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Unless otherwise indicated, these moieties preferably comprise 1 to 20 carbon atoms.

The "substituted hydrocarbyl" moieties described herein are hydrocarbyl moieties which are substituted with at least one atom other than carbon, including moieties in which a carbon chain atom is substituted with a hetero atom such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen atom. These substituents include halogen, heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyl, acyloxy, nitro, amino, amido, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The term "heteroatom" shall mean atoms other than carbon and hydrogen.

The "heterosubstituted methyl" moieties described herein are methyl groups in which the carbon atom is covalently bonded to at least one heteroatom and optionally with hydrogen, the heteroatom being, for example, a nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or halogen atom. The heteroatom may, in turn, be substituted with other atoms to form a heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, oxy, acyloxy, nitro, amino, amido, thiol, ketals, acetals, esters or ether moiety.

The "heterosubstituted acetate" moieties described herein are acetate groups in which the carbon of the methyl group is covalently bonded to at least

one heteroatom and optionally with hydrogen, the heteroatom being, for example, a nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or halogen atom. The heteroatom may, in turn, be substituted with other atoms to form a heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, oxy, acyloxy, nitro, amino, amido, thiol, ketals, acetals, esters or ether moiety.

Unless otherwise indicated, the alkyl groups described herein are preferably lower alkyl containing from one to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include methyl, ethyl, propyl, isopropyl, butyl, hexyl and the like.

Unless otherwise indicated, the alkenyl groups described herein are preferably lower alkenyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like.

Unless otherwise indicated, the alkynyl groups described herein are preferably lower alkynyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like.

The terms "aryl" or "ar" as used herein alone or as part of another group denote optionally substituted homocyclic aromatic groups, preferably monocyclic or bicyclic groups containing from 6 to 12 carbons in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl or substituted naphthyl. Phenyl and substituted phenyl are the more preferred aryl.

The terms "halogen" or "halo" as used herein alone or as part of another group refer to chlorine, bromine, fluorine, and iodine.

The terms "heterocyclo" or "heterocyclic" as used herein alone or as part of another group denote optionally substituted, fully saturated or unsaturated, monocyclic or bicyclic, aromatic or nonaromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heterocyclo group preferably has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heterocyclo include heteroaromatics such as furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary substituents include one or more of the

following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The term "heteroaromatic" as used herein alone or as part of another group denote optionally substituted aromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heteroaromatic group preferably has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heteroaromatics include furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The term "acyl," as used herein alone or as part of another group, denotes the moiety formed by removal of the hydroxyl group from the group --COOH of an organic carboxylic acid, e.g., RC(O)-, wherein R is R^1, R^1O-, R^1R^2N-, or R^1S-, R^1 is hydrocarbyl, heterosubstituted hydrocarbyl, or heterocyclo and R^2 is hydrogen, hydrocarbyl or substituted hydrocarbyl.

The term "acyloxy," as used herein alone or as part of another group, denotes an acyl group as described above bonded through an oxygen linkage (--O--), e.g., RC(O)O- wherein R is as defined in connection with the term "acyl."

Unless otherwise indicated, the alkoxycarbonyloxy moieties described herein comprise lower hydrocarbon or substituted hydrocarbon or substituted hydrocarbon moieties.

Unless otherwise indicated, the carbamoyloxy moieties described herein are derivatives of carbamic acid in which one or both of the amine hydrogens is optionally replaced by a hydrocarbyl, substituted hydrocarbyl or heterocyclo moiety.

The terms "hydroxyl protecting group" and "hydroxy protecting group" as used herein denote a group capable of protecting a free hydroxyl group ("protected hydroxyl") which, subsequent to the reaction for which protection is employed, may be removed without disturbing the remainder of the molecule. A variety of protecting groups for the hydroxyl group and the synthesis thereof may

be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981, or Fieser & Fieser. Exemplary hydroxyl protecting groups include methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, (.beta.-trimethylsilylethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloroethoxycarbonyl, t-butyl(diphenyl)silyl, trialkylsilyl, trichloromethoxycarbonyl and 2,2,2-trichloroethoxymethyl.

As used herein, “Ac” means acetyl; “Bz” means benzoyl; “Et” means ethyl; “Me” means methyl; “Ph” means phenyl; “iPr” means isopropyl; “tBu” and “t-Bu” means tert-butyl; “R” means lower alkyl unless otherwise defined; “py” means pyridine or pyridyl; “TES” means triethylsilyl; “TMS” means trimethylsilyl; “LAH” means lithium aluminum hydride; “10-DAB” means 10-desacetylbaccatin III”; “amine protecting group” includes, but is not limited to, carbamates, for example, 2,2,2-trichloroethylcarbamate or tertbutylcarbamate; “protected hydroxy” means -OP wherein P is a hydroxy protecting group; “tBuOCO” means tert-butoxycarbonyl; “tAmOCO” means tert-amyloxycarbonyl; “PhCO means phenylcarbonyl”; “2-FuCO” means 2-furylcarbonyl; “2-ThCO” means 2-thienylcarbonyl; “2-PyCO” means 2-pyridylcarbonyl; “3-PyCO” means 3-pyridylcarbonyl; “4-PyCO” means 4-pyridylcarbonyl; “C_4H_7CO” means butenylcarbonyl; “EtOCO” means ethoxycarbonyl; “ibueCO” means isobutenylcarbonyl; “iBuCO” means isobutylcarbonyl; “iBuOCO” means isobutoxycarbonyl; “iPrOCO” means isopropyloxycarbonyl; “nPrOCO” means n-propyloxycarbonyl; “nPrCO” means n-propylcarbonyl; “tC_3H_5CO” means *trans*-propenyl carbonyl;“ibue” means isobutenyl; “THF” means tetrahydrofuran; “DMAP” means 4-dimethylamino pyridine; and “LHMDS” means lithium hexamethyl disilazanide.

The following examples illustrate the invention.

Example 1

N-Debenzoyl-N-*tert*-amyloxycarbonyl-3’-desphenyl-3’-(2-furyl)-10-methoxyacetyl taxol (6515)

To a solution of N-debenzoyl-N-*tert*-amyloxycarbonyl-3’-desphenyl-3’-(2-furyl)-2’-(2-methoxy-2-propyl)-7-benzyloxycarbonyl-10-deacetyl-10-trimethylsilyl taxol (3.50 g) in 40 mL of 1:1 acetonitrile-pyridine at 0 °C (ice-water bath) was added dropwise

over 10 minutes, 10 mL of 48% aqueous hydrofluoric acid. The cooling bath was then removed and the reaction stirred at ambient temperature for 8 h, diluted with 200 mL of ethyl acetate and washed with 25 mL of water, 2 x 20 mL of saturated aqueous $NaHCO_3$ and 25 mL of saturated aqueous NaCl. The organic layer was then dried over sodium sulfate and concentrated under reduced pressure to give N-debenzoyl-N-*tert*-amyloxycarbonyl-3'-desphenyl-3'-(2-furyl)-7-benzyloxycarbonyl-10-deacetyl taxol as a white solid which was dried under high vacuum (0.1 mmHg, 12 h) and used directly in the next step.

To a solution of N-debenzoyl-N-*tert*-amyloxycarbonyl-3'-desphenyl-3'-(2-furyl)-7-benzyloxycarbonyl-10-deacetyl taxol (2.17 g, 2.293 mmol) in anhydrous methylene chloride (6 mL) was added with stirring triethylamine (1.60 mL, 11.46 mmol) followed by the dropwise addition of 0.46 mL of triethylsilyl chloride. TLC of the mixture (silica gel, 2:3 ethyl acetate:hexane) after 2 h, showed the formation of only one product. Saturated aqueous $NaHCO_3$, 2 mL was added to the reaction which was then diluted with 70 mL of ethyl acetate, washed with 10 mL of saturated aqueous $NaHCO_3$ and 15 mL of saturated aqueous NaCl. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give pure N-debenzoyl-N-*tert*-amyloxycarbonyl-3'-desphenyl-3'-(2-furyl)-2'-triethylsilyl-7-benzyloxycarbonyl-10-deacetyl taxol as a white solid (2.21 g, 91%)

To a solution of N-debenzoyl-N-*tert*-amyloxycarbonyl-3'-desphenyl-3'-(2-furyl)-2'-triethylsilyl-7-benzyloxycarbonyl-10-deacetyl taxol (660 mg, 0.622 mmol) in 4 mL anhydrous pyridine at 0 °C was added DMAP (20 mg, 0.16 mmol) under a nitrogen atmosphere. To this mixture was added drop wise methoxyacetyl chloride (220 mL, 2.489 mmol). TLC (silica gel, 2:3 ethyl acetate:hexane) after 2 h showed no starting material. The reaction was cooled to 0 °C (ice-water bath) and quenched by adding 80 mL of water.

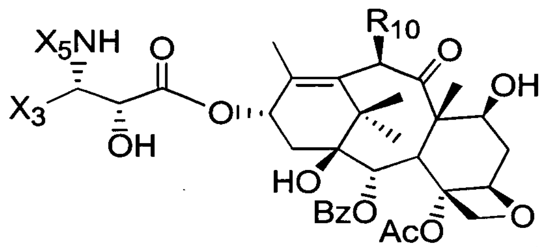
To the reaction at 0 °C (ice-water bath) was added 4 mL of acetonitrile and 2 mL of 48% aqueous hydrofluoric acid and the cooling bath was removed. The reaction was stirred at room temperature for 8.0 h, diluted with 60 mL of ethyl acetate and washed with 10 mL of saturated aqueous $NaHCO_3$ and 15 mL of saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and concentrated under reduce pressure to give 602 mg of a yellow solid which was purified by flash-chromatography (silica

gel, 1:1 ethyl acetate:hexane) to give 538 mg (85%) of pure N-debenzoyl-N-*tert*-amyloxycarbonyl-3'-desphenyl-3'-(2-furyl)-7-benzyloxycarbonyl-10-deacetyl-10-methoxyacetyl taxol (TL-650): mp 145-146 °C; Anal. Calcd. for $C_{53}H_{63}NO_{19}$: C, 62.53; H, 6.24. Found: C, 62.26; H, 6.20.

To a solution of N-debenzoyl-N-*tert*-amyloxycarbonyl-3'-desphenyl-3'-(2-furyl)-7-benzyloxycarbonyl-10-deacetyl-10-methoxyacetyl taxol (TL-650, 350 mg, 0.343 mmol) in 15 mL ethyl acetate was added 10% Pd-C (100 mg). The mixture was stirred under a H_2 atmosphere (using latex balloons) for 1 h, when TLC (silica gel, 1:1 ethyl acetate:hexane) showed no starting material. The reaction was then filtered through celite (3 g) and the celite pad washed with 25 mL of ethyl acetate. The combined organic extract was concentrated under reduced pressure to give 315 mg of a white solid which was purified by flash-chromatography (silica gel, 55:45 ethyl acetate:hexane) to give 283mg (93%) of pure N-debenzoyl-N-*tert*-amyloxycarbonyl-3'-desphenyl-3'-(2-furyl)- -10-deacetyl-10-methoxyacetyl taxol: mp 164-166 °C; ^{1}H NMR ($CDCl_3$) 8.13 (m, 2H), 7.62(m, 1H), 7.46-7.51(m, 2H), 7.41 (m, 1H), 6.41 (bs, 1H), 6.39(dd, J=3.1, 1.5 Hz, 1H), 6.25 (d, J=3.1 Hz, 1H), 6.22(dd, J=8.8, 8.7 Hz, 1H), 5.67(1H), 5.22-5.38(m, 2H), 4.98(m, 1H), 4.76(m, 1H), 4.42(m, 2H), 4.36 (d, J=9.3 Hz, 1H), 4.28(m, 1H), 4.21 (d, J=9.3 Hz, 1H), 3.82 (m, 1H), 3.42 (s, 3H), 3.41 (d, J= 5.5 Hz, 1H), 2.55-2.60(m, 1H), 2.41 (s, 3H), 2.20-2.38(m, 2H), 1.92 (s, 3H), 1.91-1.94 (m, 1H), 1.68 (bs, 3H), 1.62-1.68(m, 2H), 1.62(S, 3H), 1.36(s, 3H), 1.34(s, 3H), 1.23(s, 3H), 1.16(s, 3H), 0.80(t, J=8.2Hz, 3H); Anal. Calcd. for $C_{45}H_{57}NO_{17}.1/2H_2O$: C, 60.47; H, 6.49. Found: C, 60.64; H, 6.45.

Example 2

The procedures described in Example 1 were repeated, but other suitably protected β-lactams were substituted for the β-lactam of Example 1 to prepare the series of compounds having structural formula (13) and the combinations of substituents identified in the following table

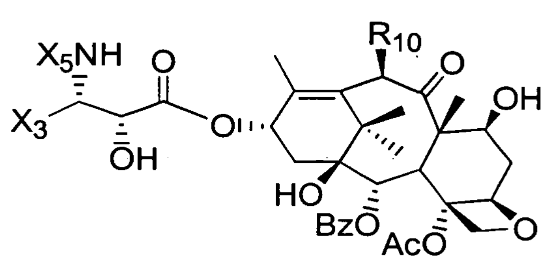


(13)

Compound	X_5	X_3	R_{10}
6577	tAmOCO	2-furyl	AcOAcO-
6515	tAmOCO	2-furyl	MeOAcO-
6066	tC_3H_5CO	2-furyl	MeOAcO-
6111	tC_3H_5CO	2-furyl	PhOAcO-

Example 3

Following the processes described in Example 1 and elsewhere herein, the following specific taxanes having structural formula 14 may be prepared, wherein R_{10} is $R_{10a}COO$- and R_{10a} is heterosubstituted methyl. In one embodiment, R_{10a} is chloromethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, phenoxymethyl, acetoxymethyl, acyloxymethyl, or methylthiomethyl.



(14)

X_5	X_3	R_{10}
tBuOCO-	2-furyl	R_{10a}COO-
tBuOCO-	3-furyl	R_{10a}COO-
tBuOCO-	2-thienyl	R_{10a}COO-
tBuOCO-	3-thienyl	R_{10a}COO-
tBuOCO-	2-pyridyl	R_{10a}COO-
tBuOCO-	3-pyridyl	R_{10a}COO-
tBuOCO-	4-pyridyl	R_{10a}COO-
tBuOCO-	isobutenyl	R_{10a}COO-
tBuOCO-	isopropyl	R_{10a}COO-
tBuOCO-	cyclopropyl	R_{10a}COO-
tBuOCO-	cyclobutyl	R_{10a}COO-
tBuOCO-	cyclopentyl	R_{10a}COO-
tBuOCO-	phenyl	R_{10a}COO-
benzoyl	2-furyl	R_{10a}COO-
benzoyl	3-furyl	R_{10a}COO-
benzoyl	2-thienyl	R_{10a}COO-
benzoyl	3-thienyl	R_{10a}COO-
benzoyl	2-pyridyl	R_{10a}COO-
benzoyl	3-pyridyl	R_{10a}COO-
benzoyl	4-pyridyl	R_{10a}COO-
benzoyl	isobutenyl	R_{10a}COO-
benzoyl	isopropyl	R_{10a}COO-
benzoyl	cyclopropyl	R_{10a}COO-
benzoyl	cyclobutyl	R_{10a}COO-
benzoyl	cyclopentyl	R_{10a}COO-
benzoyl	phenyl	R_{10a}COO-
2-FuCO-	2-furyl	R_{10a}COO-
2-FuCO-	3-furyl	R_{10a}COO-

2-FuCO-	2-thienyl	R_{10a}COO-
2-FuCO-	3-thienyl	R_{10a}COO-
2-FuCO-	2-pyridyl	R_{10a}COO-
2-FuCO-	3-pyridyl	R_{10a}COO-
2-FuCO-	4-pyridyl	R_{10a}COO-
2-FuCO-	isobutenyl	R_{10a}COO-
2-FuCO-	isopropyl	R_{10a}COO-
2-FuCO-	cyclopropyl	R_{10a}COO-
2-FuCO-	cyclobutyl	R_{10a}COO-
2-FuCO-	cyclopentyl	R_{10a}COO-
2-FuCO-	phenyl	R_{10a}COO-
2-ThCO-	2-furyl	R_{10a}COO-
2-ThCO-	3-furyl	R_{10a}COO-
2-ThCO-	2-thienyl	R_{10a}COO-
2-ThCO-	3-thienyl	R_{10a}COO-
2-ThCO-	2-pyridyl	R_{10a}COO-
2-ThCO-	3-pyridyl	R_{10a}COO-
2-ThCO-	4-pyridyl	R_{10a}COO-
2-ThCO-	isobutenyl	R_{10a}COO-
2-ThCO-	isopropyl	R_{10a}COO-
2-ThCO-	cyclopropyl	R_{10a}COO-
2-ThCO-	cyclobutyl	R_{10a}COO-
2-ThCO-	cyclopentyl	R_{10a}COO-
2-ThCO-	phenyl	R_{10a}COO-
2-PyCO-	2-furyl	R_{10a}COO-
2-PyCO-	3-furyl	R_{10a}COO-
2-PyCO-	2-thienyl	R_{10a}COO-
2-PyCO-	3-thienyl	R_{10a}COO-
2-PyCO-	2-pyridyl	R_{10a}COO-

2-PyCO-	3-pyridyl	R_{10a}COO-
2-PyCO-	4-pyridyl	R_{10a}COO-
2-PyCO-	isobutenyl	R_{10a}COO-
2-PyCO-	isopropyl	R_{10a}COO-
2-PyCO-	cyclopropyl	R_{10a}COO-
2-PyCO-	cyclobutyl	R_{10a}COO-
2-PyCO-	cyclopentyl	R_{10a}COO-
2-PyCO-	phenyl	R_{10a}COO-
3-PyCO-	2-furyl	R_{10a}COO-
3-PyCO-	3-furyl	R_{10a}COO-
3-PyCO-	2-thienyl	R_{10a}COO-
3-PyCO-	3-thienyl	R_{10a}COO-
3-PyCO-	2-pyridyl	R_{10a}COO-
3-PyCO-	3-pyridyl	R_{10a}COO-
3-PyCO-	4-pyridyl	R_{10a}COO-
3-PyCO-	isobutenyl	R_{10a}COO-
3-PyCO-	isopropyl	R_{10a}COO-
3-PyCO-	cyclopropyl	R_{10a}COO-
3-PyCO-	cyclobutyl	R_{10a}COO-
3-PyCO-	cyclopentyl	R_{10a}COO-
3-PyCO-	phenyl	R_{10a}COO-
4-PyCO-	2-furyl	R_{10a}COO-
4-PyCO-	3-furyl	R_{10a}COO-
4-PyCO-	2-thienyl	R_{10a}COO-
4-PyCO-	3-thienyl	R_{10a}COO-
4-PyCO-	2-pyridyl	R_{10a}COO-
4-PyCO-	3-pyridyl	R_{10a}COO-
4-PyCO-	4-pyridyl	R_{10a}COO-
4-PyCO-	isobutenyl	R_{10a}COO-

4-PyCO-	isopropyl	$R_{10a}COO$-
4-PyCO-	cyclopropyl	$R_{10a}COO$-
4-PyCO-	cyclobutyl	$R_{10a}COO$-
4-PyCO-	cyclopentyl	$R_{10a}COO$-
4-PyCO-	phenyl	$R_{10a}COO$-
C_4H_7CO-	2-furyl	$R_{10a}COO$-
C_4H_7CO-	3-furyl	$R_{10a}COO$-
C_4H_7CO-	2-thienyl	$R_{10a}COO$-
C_4H_7CO-	3-thienyl	$R_{10a}COO$-
C_4H_7CO-	2-pyridyl	$R_{10a}COO$-
C_4H_7CO-	3-pyridyl	$R_{10a}COO$-
C_4H_7CO-	4-pyridyl	$R_{10a}COO$-
C_4H_7CO-	isobutenyl	$R_{10a}COO$-
C_4H_7CO-	isopropyl	$R_{10a}COO$-
C_4H_7CO-	cyclopropyl	$R_{10a}COO$-
C_4H_7CO-	cyclobutyl	$R_{10a}COO$-
C_4H_7CO-	cyclopentyl	$R_{10a}COO$-
C_4H_7CO-	phenyl	$R_{10a}COO$-
EtOCO-	2-furyl	$R_{10a}COO$-
EtOCO-	3-furyl	$R_{10a}COO$-
EtOCO-	2-thienyl	$R_{10a}COO$-
EtOCO-	3-thienyl	$R_{10a}COO$-
EtOCO-	2-pyridyl	$R_{10a}COO$-
EtOCO-	3-pyridyl	$R_{10a}COO$-
EtOCO-	4-pyridyl	$R_{10a}COO$-
EtOCO-	isobutenyl	$R_{10a}COO$-
EtOCO-	isopropyl	$R_{10a}COO$-
EtOCO-	cyclopropyl	$R_{10a}COO$-
EtOCO-	cyclobutyl	$R_{10a}COO$-

EtOCO-	cyclopentyl	R_{10a}COO-
EtOCO-	phenyl	R_{10a}COO-
ibueCO-	2-furyl	R_{10a}COO-
ibueCO-	3-furyl	R_{10a}COO-
ibueCO-	2-thienyl	R_{10a}COO-
ibueCO-	3-thienyl	R_{10a}COO-
ibueCO-	2-pyridyl	R_{10a}COO-
ibueCO-	3-pyridyl	R_{10a}COO-
ibueCO-	4-pyridyl	R_{10a}COO-
ibueCO-	isobutenyl	R_{10a}COO-
ibueCO-	isopropyl	R_{10a}COO-
ibueCO-	cyclopropyl	R_{10a}COO-
ibueCO-	cyclobutyl	R_{10a}COO-
ibueCO-	cyclopentyl	R_{10a}COO-
ibueCO-	phenyl	R_{10a}COO-
iBuCO-	2-furyl	R_{10a}COO-
iBuCO-	3-furyl	R_{10a}COO-
iBuCO-	2-thienyl	R_{10a}COO-
iBuCO-	3-thienyl	R_{10a}COO-
iBuCO-	2-pyridyl	R_{10a}COO-
iBuCO-	3-pyridyl	R_{10a}COO-
iBuCO-	4-pyridyl	R_{10a}COO-
iBuCO-	isobutenyl	R_{10a}COO-
iBuCO-	isopropyl	R_{10a}COO-
iBuCO-	cyclopropyl	R_{10a}COO-
iBuCO-	cyclobutyl	R_{10a}COO-
iBuCO-	cyclopentyl	R_{10a}COO-
iBuCO-	phenyl	R_{10a}COO-
iBuOCO-	2-furyl	R_{10a}COO-

iBuOCO-	3-furyl	$R_{10a}COO$-
iBuOCO-	2-thienyl	$R_{10a}COO$-
iBuOCO-	3-thienyl	$R_{10a}COO$-
iBuOCO-	2-pyridyl	$R_{10a}COO$-
iBuOCO-	3-pyridyl	$R_{10a}COO$-
iBuOCO-	4-pyridyl	$R_{10a}COO$-
iBuOCO-	isobutenyl	$R_{10a}COO$-
iBuOCO-	isopropyl	$R_{10a}COO$-
iBuOCO-	cyclopropyl	$R_{10a}COO$-
iBuOCO-	cyclobutyl	$R_{10a}COO$-
iBuOCO-	cyclopentyl	$R_{10a}COO$-
iBuOCO-	phenyl	$R_{10a}COO$-
iPrOCO-	2-furyl	$R_{10a}COO$-
iPrOCO-	3-furyl	$R_{10a}COO$-
iPrOCO-	2-thienyl	$R_{10a}COO$-
iPrOCO-	3-thienyl	$R_{10a}COO$-
iPrOCO-	2-pyridyl	$R_{10a}COO$-
iPrOCO-	3-pyridyl	$R_{10a}COO$-
iPrOCO-	4-pyridyl	$R_{10a}COO$-
iPrOCO-	isobutenyl	$R_{10a}COO$-
iPrOCO-	isopropyl	$R_{10a}COO$-
iPrOCO-	cyclopropyl	$R_{10a}COO$-
iPrOCO-	cyclobutyl	$R_{10a}COO$-
iPrOCO-	cyclopentyl	$R_{10a}COO$-
iPrOCO-	phenyl	$R_{10a}COO$-
nPrOCO-	2-furyl	$R_{10a}COO$-
nPrOCO-	3-furyl	$R_{10a}COO$-
nPrOCO-	2-thienyl	$R_{10a}COO$-
nPrOCO-	3-thienyl	$R_{10a}COO$-

nPrOCO-	2-pyridyl	$R_{10a}COO$-
nPrOCO-	3-pyridyl	$R_{10a}COO$-
nPrOCO-	4-pyridyl	$R_{10a}COO$-
nPrOCO-	isobutenyl	$R_{10a}COO$-
nPrOCO-	isopropyl	$R_{10a}COO$-
nPrOCO-	cyclopropyl	$R_{10a}COO$-
nPrOCO-	cyclobutyl	$R_{10a}COO$-
nPrOCO-	cyclopentyl	$R_{10a}COO$-
nPrOCO-	phenyl	$R_{10a}COO$-
nPrCO-	2-furyl	$R_{10a}COO$-
nPrCO-	3-furyl	$R_{10a}COO$-
nPrCO-	2-thienyl	$R_{10a}COO$-
nPrCO-	3-thienyl	$R_{10a}COO$-
nPrCO-	2-pyridyl	$R_{10a}COO$-
nPrCO-	3-pyridyl	$R_{10a}COO$-
nPrCO-	4-pyridyl	$R_{10a}COO$-
nPrCO-	isobutenyl	$R_{10a}COO$-
nPrCO-	isopropyl	$R_{10a}COO$-
nPrCO-	cyclopropyl	$R_{10a}COO$-
nPrCO-	cyclobutyl	$R_{10a}COO$-
nPrCO-	cyclopentyl	$R_{10a}COO$-
nPrCO-	phenyl	$R_{10a}COO$-

Example 4

Following the processes described in Example 1 and elsewhere herein, the following specific taxanes having structural formula 15 may be prepared, wherein R_7 is hydroxy and R_{10} in each of the series (that is, each of series "A" through "K") is as previously defined, including wherein R_{10} is $R_{10a}COO$- wherein R_{10a} is a heterosubstituted methyl moiety lacking a carbon atom which is in the beta position relative to the carbon atom of which R_{10a} is a substituent. The heterosubstituted

methyl is covalently bonded to at least one heteroatom and optionally with hydrogen, the heteroatom being, for example, a nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or halogen atom. The heteroatom may, in turn, be substituted with other atoms to form a heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, oxy, acyloxy, nitro, amino, amido, thiol, ketals, acetals, esters or ether moiety. Exemplary R_{10} substituents include $R_{10a}COO$- wherein R_{10a} is chloromethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, phenoxymethyl, acetoxymethyl, acyloxymethyl, or methylthiomethyl.

In the "A" series of compounds, X_{10} is as otherwise as defined herein. Preferably, heterocyclo is substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), and R_7 and R_{10} each have the beta stereochemical configuration.

In the "B" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7 and R_{10} each have the beta stereochemical configuration.

In the "C" series of compounds, X_{10} and R_{9a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{9a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

In the "D" and "E" series of compounds, X_{10} is as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or

lower alkyl (e.g., tert-butyl), and R_7, R_9 (series D only) and R_{10} each have the beta stereochemical configuration.

In the "F" series of compounds, X_{10}, R_{2a} and R_{9a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

In the "G" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

In the "H" series of compounds, X_{10} is as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7 and R_{10} each have the beta stereochemical configuration.

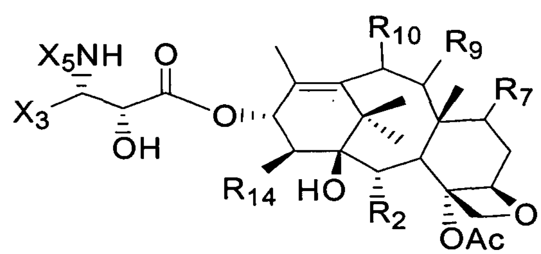
In the "I" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7 and R_{10} each have the beta stereochemical configuration.

In the "J" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

In the "K" series of compounds, X_{10}, R_{2a} and R_{9a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl,

or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

Any substituents of each X_3, X_5, R_2, R_7, and R_9 may be hydrocarbyl or any of the heteroatom containing substituents selected from the group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.



(15)

Series	X_5	X_3	R_{10}	R_2	R_9	R_{14}
A1	$-COOX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	O	H
A2	$-COX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	O	H
A3	$-CONHX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	O	H
A4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	O	H
A5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	O	H
A6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	O	H
A7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	O	H
A8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	O	H

A9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	O	H
A10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	O	H
A11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	O	H
A12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	O	H
B1	$-COOX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	O	H
B2	$-COX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	O	H
B3	$-CONHX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	O	H
B4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	O	H
B5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	O	H
B6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	O	H
B7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	O	H
B8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	O	H
B9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	O	H
B10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	O	H
B11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	O	H

B12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	O	H
C1	$-COOX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C2	$-COX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C3	$-CONHX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
D1	$-COOX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	OH	H
D2	$-COX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	OH	H
D3	$-CONHX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	OH	H
D4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	OH	H

D5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	OH	H
D6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	OH	H
D7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	OH	H
D8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	OH	H
D9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	OH	H
D10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	OH	H
D11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	OH	H
D12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	OH	H
E1	$-COOX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	O	OH
E2	$-COX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	O	OH
E3	$-CONHX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	O	OH
E4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	O	OH
E5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	O	OH
E6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	O	OH
E7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	O	OH

E8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	O	OH
E9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	O	OH
E10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	O	OH
E11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	O	OH
E12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	O	OH
F1	$-COOX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F2	$-COX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F3	$-CONHX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H

F11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
G1	$-COOX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
G2	$-COX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
G3	$-CONHX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
G4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
G5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
G6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
G7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
G8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
G9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
G10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
G11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
G12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	H
H1	$-COOX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	OH	OH
H2	$-COX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	OH	OH
H3	$-CONHX_{10}$	heterocyclo	$R_{10a}COO-$	C_6H_5COO-	OH	OH

H4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	OH	OH
H5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	OH	OH
H6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	C_6H_5COO-	OH	OH
H7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	OH	OH
H8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	OH	OH
H9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	C_6H_5COO-	OH	OH
H10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	OH	OH
H11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	OH	OH
H12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	C_6H_5COO-	OH	OH
I1	$-COOX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	O	OH
I2	$-COX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	O	OH
I3	$-CONHX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	O	OH
I4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	O	OH
I5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	O	OH
I6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	O	OH

I7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	O	OH
I8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	O	OH
I9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	O	OH
I10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	O	OH
I11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	O	OH
I12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	O	OH
J1	$-COOX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH
J2	$-COX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH
J3	$-CONHX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH
J4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH
J5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH
J6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH
J7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH
J8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH
J9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH

J10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH
J11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH
J12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	OH	OH
K1	$-COOX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K2	$-COX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K3	$-CONHX_{10}$	heterocyclo	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{10a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH

Example 5

In Vitro cytotoxicity measured by the cell colony formation assay

Four hundred cells (HCT116) were plated in 60 mm Petri dishes containing 2.7 mL of medium (modified McCoy's 5a medium containing 10% fetal bovine serum and 100 units/mL penicillin and 100 g/mL streptomycin). The cells were incubated in a CO_2 incubator at 37 °C for 5 h for attachment to the bottom of Petri dishes. The compounds identified in Example 2 were made up fresh in medium at ten times the final concentration, and then 0.3 mL of this stock solution was added to the 2.7 mL of medium in the dish. The cells were then incubated with drugs for 72 h at 37 ° C. At the end of incubation the drug-containing media were decanted, the dishes were rinsed with 4 mL of Hank's Balance Salt Solution (HBSS), 5 mL of fresh medium was added, and the dishes were returned to the incubator for colony formation. The cell colonies were counted using a colony counter after incubation for 7 days. Cell survival was calculated and the values of ID50 (the drug concentration producing 50% inhibition of colony formation) were determined for each tested compound.

Compound	**IN VITRO ID 50 (nm) HCT116**
taxol	2.1
docetaxel	0.6
6577	<1
6515	<1
6066	<1
6111	<1